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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,371	01/16/2007	Alan Cuthbertson	PZ0382	3817

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,371	CUTHBERTSON ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3,11,13 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,12 and 16-36* is/are rejected.

7)☒ Claim(s) *36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending and are subject of this office action. Receipt is acknowledged of a preliminary amendment filed on 12/12/2005 in which claims 2-6, 8, 10, 14, 16, 18, 19, 24, 25, and 29 and 31-36-were amended.

Claims 3, 11 and 13-15 are withdrawn as being drawn to non-elected specie. Claims 1-2, 4-10, 12, 16-36 are under consideration in the instant action.

Priority information

This application claims foreign priority to GB 0326546.9 dated Nov 14th 2003. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 12/12/2005. The Examiner has considered the reference cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

The "Great Britain Search Report " on the 1449 dated 02-2005 has been lined out because it is not a published document and therefore cannot have a date of publication which is required for a citation in the non-patent document area of 1449.

Election/Restrictions

Applicants' election with traverse of compound 24A labeled with an imaging moiety which is 123I (a gamma-emitting radio-halogen) from the instant disclosure on 04/01/2008 is acknowledged.

Applicants' traverse the Examiner's holding that the claims lack unity on the grounds that the technical feature of the claimed invention is an MMP inhibitor that is covalently attached to an imaging moiety, not an MMP inhibitor per se. This argument is not persuasive because the claimed MMP inhibitors were known in the art at the time of the invention as evidenced by EP 1 088 550 A1, cited by Applicants, Note that EP '550 teaches at page 10, [0043] that one can isotopically label the compounds (MMP inhibitors) of the invention. Thus, MMP inhibitors having the structures recited in the instant claims labeled with a radioisotope, were known in the art at the time of the invention.

Instant claims 3, 11 and 13-15 are withdrawn as being drawn to non-elected specie.

The restriction/election requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 36 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 36 does not appear to further limit claim 1 from which it depends because claim 1 claims an imaging agent per se. As such, it doesn't matter what the imaging agent is used for and claim 36 does not further limit the structure of the imaging agents of claim 1 in any way.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34-35 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the

reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, Claim 32 recites a genus of "derivatives". There is insufficient evidence for derivatives as claimed in the instant disclosure. The 10th edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as, "a chemical substance related structurally to another substance and theoretically derivable from it." For example, carbon dioxide could theoretically be derived from the combustion of alkyl halide which would be considered an alkyl halide derivative. Therefore, the definition of derivative in the Merriam-Webster Collegiate Dictionary does not shed light on what Applicants' intended for the meaning of a "organometallic *derivative* or alkyl halide *derivative* or a *derivative* containing a functional group which undergoes facile alkylation" as recited in instant claim 32. Instant disclosure does not provide adequate support for all the possible derivatives encompassed by the claim.

Accordingly, for an ordinarily skilled artisan to test every derivative of the claimed compounds would impose undue burden. The need for testing amongst varying species of compounds to determine the full scope of the genus of derivatives as instantly claimed demonstrates that applicants were not in possession of the full scope of the genus now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by

disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163. Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other agents that may have any of the disclosed functions, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention. It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other agents that may be amenable for use in the present invention, it remains that at the time of the invention Applicants had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

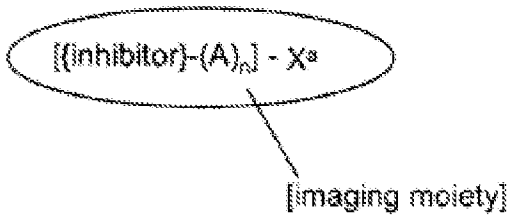
Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. Claim 6 recites the imaging agent of Claim 1, where the imaging agent is of formula II as follows:



(II)

In the formula (II) above [imaging moiety] points to $(A)_n$ and in the claim under the formula (II), $(A)_n$ is described as follows:

> -$(A)_n$- is a linker group wherein each A is independently -CR_2- , -CR=CR- , -C≡C- , -CR_2CO_2- , -CO_2CR_2- , -NRCO- , -CONR- , -NR(C=O)NR-, -NR(C=S)NR-, -SO_2NR- , -$NRSO_2$- , -CR_2OCR_2- , -CR_2SCR_2- , -CR_2NRCR_2- , a C_{4-8} cycloheteroalkylene group, a C_{4-8}

Additionally, X^a is defined as the imaging moiety in this claim which does not match the label in the picture. As such, the claims are unclear with regard to where the imaging moiety is attached in the recited structures and further unclear whether [imaging moiety] is a different entity than the X^a substituent that is also recited as an imaging moiety in the claims.

Instant claims 8-10, 12, 22, and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 8 and 22 recites the limitation “the radioactive metal ion or paramagnetic metal ion” in the claims. There is insufficient antecedent basis for this limitation in the claims. It would be remedial to amend the claims to provide a clear

antecedent basis for the term “radioactive metal ion or paramagnetic metal ion”. Claims dependent from claims 8 and 22 are included in this rejection.

Instant claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 23 is drawn towards a conjugate dependent on claim 20, of formula IIb. Claim 20 is drawn towards the radiopharmaceutical composition of claim 19, where the imaging moiety comprises a radioactive metal ion. The dependency of claim 23 is unclear and thereby renders it indefinite. Additionally, claim 23 refers to the definitions of the terms A, n and X^a in the formula (IIb) as defined by Claim 6. The formula (II) in Claim 6 points to A_n as an imaging moiety where as A_n in formula (IIb) in claim 23 is labeled as Ligand. It would be remedial to amend the claims and the formulae addressing this discrepancy.

Instant claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 32, the phrase "such as" in section (i) of the claim renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 34-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 34-35 provide for the use of the imaging agent but, since the claims do not set forth any steps

involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

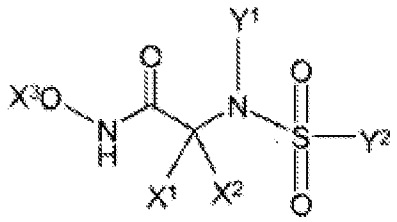
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of

35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-2, 4-10, 12, 16-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al (WO 01/60416) or Mobasherry (WO 01/92244) in view of Sahagan (EP 1088550, referenced in the IDS)

The instant claims are drawn towards an imaging agent which comprises a metalloproteinase inhibitor of formula (I) labeled with an imaging moiety which can be detected following administration of said labeled matrix metalloproteinase inhibitor to the mammalian body *in vivo*.



(I)

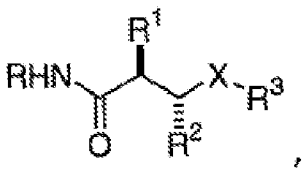
Further limitations include, the imaging agent wherein the imaging moiety is chosen from a radioactive metal ion, paramagnetic metal ion etc (instant claim 5, 8-13), imaging agent is of formula II (instant claims 6-7), a pharmaceutical composition of the imaging agent of claim 1 (instant claims 18-21), A conjugate of the MMP of formula (I) with a ligand (claims 22-26) and a kit for the preparation of the radiopharmaceutical composition (claims 27-33).

With reference to instant claims 34-36, applicant is claiming the imaging agent of Claim 1, the limitation wherein the imaging agent is used for the diagnosis of artherosclerosis, unstable plaques or intravascular diseases are

intended uses of the imaging agent and will be given little patentability weight in the absence of a showing that such claimed intended uses result in a material difference in the claimed compositions.

Carpenter teaches diagnostic agents comprising a diagnostic metal and a compound, wherein the compound comprises: 1:10 targeting moieties; a chelator, and 0-1 linking groups between the targeting moiety and chelator; wherein the targeting moiety is a matrix metalloproteinase (MMP) inhibitor; and wherein the chelator is capable of conjugating to the diagnostic metal (abstract and page 143, claim 1). Carpenter teaches that imaging agents targeted to one or more MMP's would be very useful in detecting and monitoring the degree of extracellular matrix degradation in congestive heart failure, artherosclerosis and other degradative disease processes and these imaging agents, containing a ligand directed at one or more MMP, will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases (page 5, lines 8-15).

With regard to instant claims 1, 2, 4 and 16-17, Carpenter teaches the details of targeting molecules in his inventions that are MMP inhibitors which are structurally similar to the instantly claimed compounds of formula (I) (page 143-150, claims 4-12 and page 176-188, claims 53-68). For example, one of the compounds claimed in claim 31 is as follows:



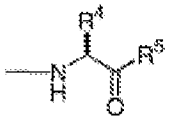
Wherein:

R is independently OH or $-CH_2SH$;

R^1 is independently selected at each occurrence from the group: H, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, and heterocycle-S-CH_2-;

R^2 is independently C_{1-20} alkyl;

X is independently C=O or SO_2, provided when X is C=O, R^3 is



, and when X is SO_2, R^3 is independently selected from the group: aryl substituted with 0-2 R^6, and heterocycle substituted with 0-2 R^6;

R^4 is independently selected at each occurrence from the group: C_{1-6} alkyl, phenyl, and benzyl;

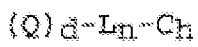
R^5 is independently at each occurrence from the group: NH(C_{1-6} alkyl), NH-phenyl, and NH-heterocycle; wherein said alkyl, phenyl and heterocycle groups are optionally substituted with a bond to L_m;

R^6 is independently aryloxy substituted with 0-3 R^7;

R^7 is independently halogen or methoxy;

With regards to claim 5 Carpenter teaches that the imaging agent may be a MMP inhibitor linked to radioisotope which are known to be useful for imaging by gamma scintigraphy or positron emission tomography (PET) (page 6, lines 15-18) .

With regards to instant claims 6-9 Carpenter teaches a diagnostic agent according having the formula



Where Q is the compound of formula (Ia) or (Ib) which is the matrix metalloproteinase inhibitor; Ln is a linking group and Ch is a metal bonding unit (chelator) which binds to the (pages 163-171, claim 31).

With regards to instant claims 8, 10 Carpenter teaches the diagnostic agent wherein the diagnostic metal is selected from a group consisting of a paramagnetic metal, a ferromagnetic metal, a gamma-emitting radioisotope or an X-ray absorber (page 174, claim 36) and teaches wherein the diagnostic metal is radioisotope selected from the group consisting of ^{99m}Tc, 9^{5}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga and ^{68}Ga. (page 174, claims 37-40).

With regards to instant claims 12, although Carpenter does not explicitly teach the limitations of instant claims 12, Carpenter's teachings of using a radioisotope useful for imaging by gamma scintigraphy or positron emission tomography (page 6, line 15-18) renders this claim obvious.

With regards to instant claims 18-21 Carpenter teaches a diagnostic composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier (page 175, claim 43)

With regards to claims 22-26 Carpenter teaches groups which can be used as linkers between the targeting moieties and the chelator (pages 150-155,

claims 13-22) and the chelator with a metal bonding units (page 155-163, claims 23-30) which can be used in his invention.

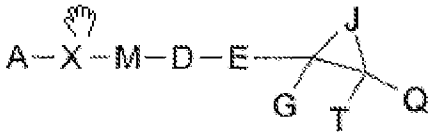
With regards to instant claims 27-33 Carpenter teaches a kit comprising a compound of Claim 1, with one or more ancillary ligands and a reducing agent (page 175, claims 44-47). Although Carpenter does not teach the exclusive limitations of instant claims 27-33, Carpenter teaches the kit comprising of a ligand and a reducing agent and it is obvious to one of ordinary skilled in the art to generate a kit with the components required for generation of the final product.

With regards to instant claims 34-36 Carpenter teaches a method of detecting, imaging or monitoring artherosclerosis in a patient by administering a diagnostic agent of claim 1 and acquiring an image of the site of concentration of said diagnostic agent (page 204, claims 95-98).

Accordingly, Carpenter provides one of ordinary skill in the art motivation to prepare an imaging agent by synthesizing compounds structurally similar to those taught by carpenter, attach an imaging moiety to the compound with or without a linker, prepare compositions and kits of the imaging agent and use it in the diagnosis of cardiovascular diseases especially artherosclerosis.

Mobashery also teaches compounds that inhibit matrix metalloproteinase in *vivo* and in *vitro;* and a method for imaging a tumor *vivo* or *vitro* (abstract).

With regards to instant claims 1,2, 4, 16 and 17 Mobashery teaches compounds of formula (I)



(I)

wherein

A-X-M is a hydrophobic group;

D is O, S, (C_1-C_6)alkyl, a direct bond, SO_2, SO, C(=O)NR, C(=O)O, NRC(=O), or OC(=O);

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl, wherein any alkyl, cycloalkyl, alkenyl, or alkynyl of E is optionally substituted with one or more (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, cyano, nitro, halo, SR, NRR, or COOR, wherein each R is independently H or (C_1-C_6)alkyl;

J is S or O;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

or a pharmaceutically acceptable salt thereof.

which are structurally related to the instantly claimed compounds (pages 44-45, claims 1-4).

With regards to instant claims 5, 8, 10 and 12 Mobashery teaches that the radiolabeled compounds of formula (I) are also useful as imaging agents for imaging cells comprising MMP's. Accordingly, the invention also provides compounds of formula (I) that include one or more detectable radionuclides which can be incorporated into the compound by replacing an atom of the compound of formula(I) with a radionuclide (e.g. nonmetallic radionuclide) or the radiolabeled compound can be prepared by linking a compound of formula (I) to a chelating group that includes a detectable radionuclide which renders these claims obvious (page 20, lines 8-19; pages 48-48, claims 25-30). Mobashery

teaches the "detectable radionuclide" as any suitable radionuclide useful in a diagnostic procedure in vivo or in vitro and suitable detectable radionuclides include metallic radionuclides and non-metallic radionuclides (page 21, lines 3-7) Mobashery additionally teaches that the non-metallic radionuclide can be a non-metallic paramagnetic atom (e.g., Fluorine-19); or a non-metallic positron emitting radionuclide (e.g., Carbon-11, Iodine-123) (page 20, lines 31-33) (page 49-50, claims 25-30)

With regards to instant claims 6-9 Mobashery teaches that the “chelating group” is a group that includes a detectable radionuclide and any suitable chelating group can be employed. In addition Mobashery provides several references which discloses suitable chelating groups (page 20, lines 19—page 21, line 2).

With regards to instant claims 18-21 Mobashery teaches the pharmaceutical compositions of the compounds of formula (I) that comprises a radiolabeled compound of formula (I) and a pharmaceutically acceptable carrier (page 5, lines 25-27 and page 26, lines 6-13, page 49, claim 24 and page 50, claim 31).

With regards to instant claims 22-26 Mobashery teaches a combination of the compound of his invention with a chelating group comprising a detectable radionuclide (page 50, claim 28).

With regards to instant claims 34-36 Mobashery also provides a compound of formula (I) that comprises a radionuclide, or a pharmaceutically acceptable salt thereof for use in medical diagnosis which includes processes

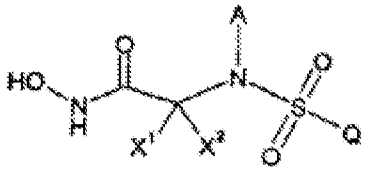
involving modulation of MMP activity such as angiogenesis, inflammation, cardiovascular diseases etc. (page 6, lines 5-10).

Accordingly Mobashery provides one of ordinary skills in the art motivation to develop matrix metalloproteinase inhibitors conjugated to a detectable moiety for use in diagnosis of diseases associated with MMP activity.

What both Carpenter and Mobashery do not teach is the radio labeling of the specific matrix metalloproteinase inhibitors of the formula recited in the instant claims.

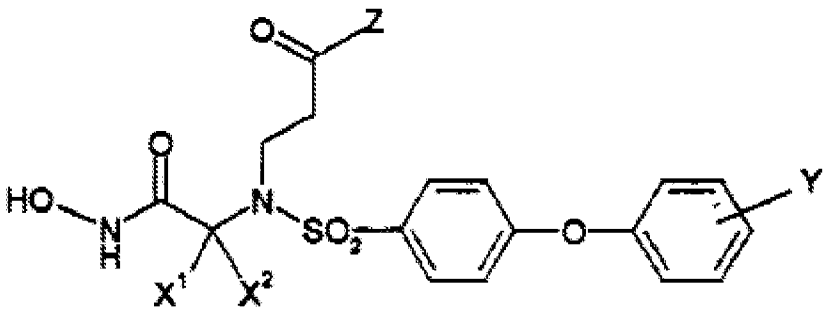
This deficiency is cured by the teachings of Sahagan et al.

Sahagan teaches methods of using a compound of formula (I) (abstract, claim 1, page).



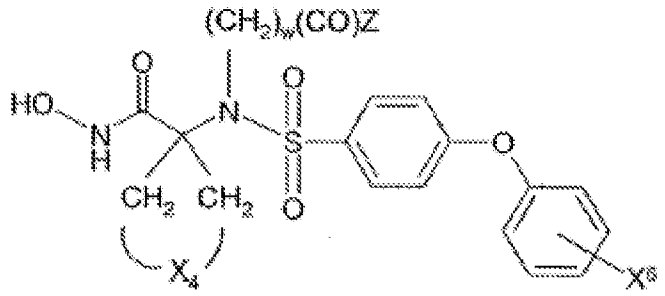
(I)

Substituents for the variables in the formula (I) above as taught by Sahagan reads on the matrix metalloproteinase inhibitors claimed in the instant applications. Sahagan teaches that one preferred methods of the invention comprise the administration of the formula (Ic) below (lines 1-10, page 5):



(Ic)

which is structurally similar to the instantly claimed compound (V)



(V)

Sahagan teaches that the compounds of his invention are inhibitors of zinc matrix metalloendopeptidases especially those belonging to the matrix metalloproteinase (MMP) (page 2, paragraph [0002]) and can be used to treat several diseases which are characterized by metalloproteinase activity (page 10, paragraph [0045]). Accordingly, Sahagan is drawn to the same class of compounds disclosed in Carpenter and Mobashery.

Sahagan teaches that the method of treatment as per his invention also includes isotopically-labeled compounds, which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different form the atomic mass or mass number usually found in nature. Additionally, Sahagan teaches that the compounds relating to the present invention, prodrugs thereof , and pharmaceutically acceptable salts of said compounds or of said prodrugs which contains the isotopes are within the scope of his invention (page 10, paragraph [0043]).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. It would have been *prima facie* obvious to the skilled artisan to develop diagnostic imaging agents comprising a matrix metalloproteinase inhibitors taught by Sahagan conjugated to an imaging moiety as taught by Carpenter or Mobasherry. An ordinarily skilled artisan would have been motivated to use matrix metalloproteinase inhibitors compound taught in the prior art and conjugate it to a radioactive imaging moiety through a linker or a chelator for use in diagnosis of cardiovascular diseases since the prior art as taught by Carpenter and Mobashery have already shown that these compounds can be successfully used for diagnostic purposes when conjugated to an imaging moiety. Furthermore, using the imaging agents to develop a pharmaceutical composition or kit would have been obvious to one of ordinary skill in the art at the time of invention since the prior art teaches compositions and kits developed using similar compounds.

A skilled artisan will be able to develop such a dosage form with a reasonable expectation of success based on the state of the art at the time of invention in order to provide imaging agents comprising a matrix metalloproteinase inhibitors conjugated to an imaging moiety for diagnosis of cardiovascular diseases, since the imaging of MMP's in the heart would be useful for the localization and monitoring the progression/regression of a variety of

cardiac diseases which are associated with alterations in the MMP content of the cardiac tissues.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

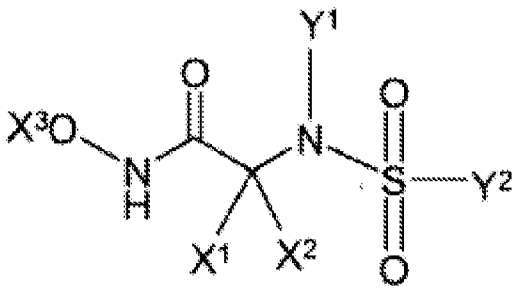
invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

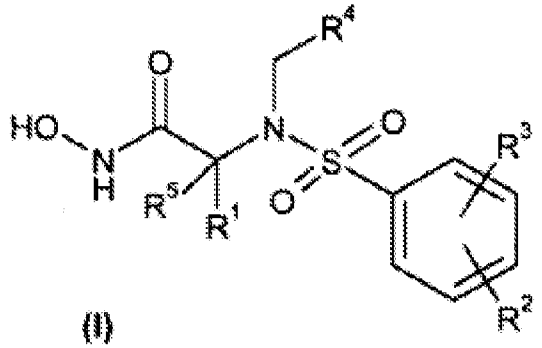
Claims 1-2, 4-10, 12, 16-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-21, 24-28, 30-31, 35 of copending Application No. 10544945 (copending '945). Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 1 is generic to the compound that is recited in claim 1 of copending '945. That is, claim 1 if copending '945 falls entirely within the scope of claim 1 or, in other words, instant claim 1 is anticipated by claim 1of copending '945. Specifically, the compound of claim 1 of the copending '945 is the compound of instant claim 1 where in the formula $[A^1]_p[O]_qA^2$ for Y^2 p=0 and q=0 and A2 is C_{6-10} aryl. Instant claims compare to the copending '945 as follows:

1. Claims 1-4, 6 and 14-17 of instant application are drawn to an imaging agent which comprises a metalloproteinase inhibitor of general Formula (I) (shown below) labeled with an imaging moiety.



(I)

Claim 1-4 of co-pending '945 recites a diagnostic imaging agent which comprises a matrix metalloproteinase inhibitor of formula I (shown below) labeled with a γ-emitting radionuclide.



(I)

The specific compound claimed in the composition of claims 1-18 of copending ‘945 is a specie of the genus of compounds claimed in the composition of instant claims 1-19 and 22-26.

2. In the instant application claims 5, 7 and 10-12 recites the specifics of the imaging moiety of the imaging agent claimed in instant claim 1. Claims 5, 7-9, 10-14 of copending '945 recites similar limitations with reference to the imaging moiety of the diagnostic imaging agent claimed in copending ‘945 claim 1.

3. Claims 8-9, 22-26 of the instant application recites the limitations with reference to the ligand and the conjugate of imaging agent claimed in instant claim1. Claims 15-18 of copending ‘945 recites similar limitations with reference to the ligand and the conjugate of diagnostic imaging agent claimed in copending '945 claim 1.

4. Claims 18-21 of the instant application are drawn towards pharmaceutical or radiopharmaceutical compositions which comprises the imaging agent of instant claim 1. Claims 19-21 of copending ‘945 are drawn towards a pharmaceutical composition comprising the diagnostic imaging agent of copending '945 claim 1.

5. Claims 27, 29-32 of the instant application are drawn to a kit for the preparation of the radiopharmaceutical composition of instant claims 20-21. Claims 24-28 and 35 of copending '945 are drawn to a kit for the preparation of the pharmaceutical composition of copending claims 19-20.

6. Claims 34-36 of the instant application is drawn to the imaging agent being used for the diagnostic imaging of arthrosclerosis, unstable plaques and for

intravascular detection of atherosclerosis. Claims 30 and 31 of copending'945 are drawn towards the used of the pharmaceutical composition fro the diagnostic imaging of cardiovascular disease such as atherosclerosis.

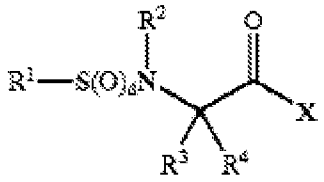
Therefore subject matter disclosed in claims 1-2, 4-10, 12, 16-36 of the instant application is fully taught in claims 1-21, 24-28 and 35 of copending '945 and are hereby rejected under the judicially created doctrine of obviousness-type double patenting

Conclusion

Claims 1-2, 4-10, 12, 16-36 are rejected. No claims are allowed

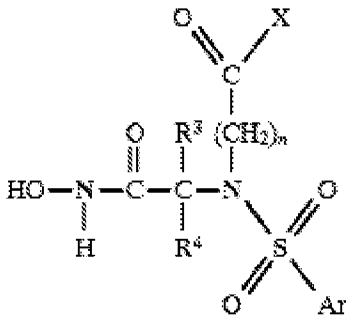
The prior art made of record and not relied upon is considered pertinent to applicant's disclosure are as follows:

a) Conrad et al. (US 6677355) which teaches compounds of the formula 1 shown below,

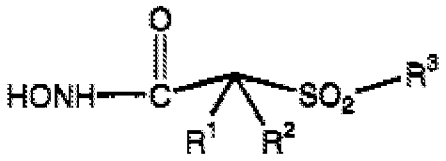


Which are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such prevent or treat diseases resulting from the breakdown of connective tissues.

b. Robinson et. al. (US 5863949)) which provides compounds of formula (I) useful in the treatment of a condition selected from the group consisting of arthritis cancer, tissue ulceration, etc.



c. Barta et al (WO 00/69821) drawn towards treatment process that comprises administering an effective amount of an aromatic sulfone hydroxamic acid that exhibits excellent inhibitory activity of one or more matrix metalloproteinase enzymes. A contemplated compound corresponds in structure to formula (I) below:



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Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 8 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SAVITHA RAO
Examiner
Art Unit 4131

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614